REMARKS

In response to the office action of February 26, 2008, Applicants have amended the claims, which when considered with the following remarks, is deemed to advance prosecution of this application. Favorable consideration of presently pending, elected claims 2 and 13 is respectfully requested.

Claims 2 and 13 have been rejected under 35 U.S.C. 102(e) as allegedly anticipated by WO 01/95928. WO '928 has been cited for allegedly teaching a method of inducing hematopoietic chimerism in a recipient comprising the steps of administering bone marrow cells, an anti-LFA inhibitor, and a co-stimulation inhibitor (anti-CD28 or anti-CD40/CD154) and immunosuppressant.

Applicants submit that the teaching of WO '928 is limited to a method to regulate cell-mediated immune responses after antigen presentation, e.g., to suppress graft rejection after transplantation of tissues. *See e.g.*, page 20, lines 6-9. The method involves the steps of administering to a subject at least three agents. The first agent is a molecule that recognizes and binds the CE28, CTLA4 or B7 molecules on lymphocytes. The second agent used in the method is a molecule that recognizes and binds CD40 or CD154 on lymphocytes, and the third agent is a molecule that interferes with LFA-1 adhesion to its ligands.

WO '928 does not teach or suggest the *additional* administration of bone marrow cells or other precursor cells to a recipient of cells, tissue or an organ transplant.

As presently amended, claim 2 recites: "A method for inducing hematopoietic chimerism in a recipient of cells, tissue or an organ transplant from a donor comprising additionally administering to the recipient

i) bone marrow cells or other precursor cells from the donor; and

ii) an anti- LFA-1 antibody in combination with at least one co-agent selected from an anti-CD154 antibody and 40-O-(2-hydroxyethyl)-rapamycin."

Claim 2 thus recites a preferred embodiment of the invention and find support throughout the specification, e.g., page 15, last paragraph of PCT/EP2003/008436. Presently amended claim 2 does not require a molecule that binds CE28, CTLA4 or B7 molecule on lymphocytes.

Accordingly, claim 2 and claim 13 (which depends from claim 2) are distinguished from the teaching of WO '928. Withdrawal of the rejection of claims 2 and 13 under 35 U.S.C.§ 102(e) is therefore warranted.

Claims 2 and 13 have been rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over US Patent 6,653,282 or WO 95/34320 each in view of US Patent 6,486,209 and US 2002/01524900.

'282 has been cited for allegedly teaching a method of inducing immune tolerance during organ, tissue or cell transplantation, including bone barrow transplantation. The method comprises administering to the subject a combined therapy of an LFA-1 inhibitor and costimulatory inhibitor such as anti-CD28 or anti-CD40/CD154. '282 does not teach or suggest the additional administration of bone marrow cells or other precursor cells to a recipient of cells, tissue or an organ transplant.

WO '320 has been cited for allegedly teaching a method of inducing immune tolerance during organ, tissue or cell transplantation, including bone marrow transplantation. The method involves administering to the subject a combined therapy of an LFA-1 inhibitor and costimulatory signal in an antigen specific T cell, such as a soluble form of CTLA4 or an anti-B7 or anti-B7-2 antibody. *See* page 3 of '320. Use of an antiCD154 antibody is not taught by '320. The sentence bridging pages 3 and 4 of WO '320 teaches that donor cells e.g., bone marrow cells are contacted with the first and second agents *in vitro* in the presence of recipient cells prior to transplantation of the donor cells into the recipient. Page 4 of WO '320 further teaches that donor cells such as hematopoietic cells may be administered to the recipient as a priming step *prior* to transplantation of the graft.

With respect to claim 13, the examiner admits that US '282 or WO'320 does not teach a method of inducing hematopoietic chimerism comprising administering a combination of LFA-1 inhibitor, co-stimulation inhibitor and immunosuppressive inhibitor 15-deoxyspergualine. However, the examiner has cited US '209 for teaching a method of transplantation of organ, tissue or cell comprising administering to the subject the immunosuppressive inhibitor 15-deoxyspergualine.

US '490 has been cited for teaching a method of inducing hematopoietic chimerism in a subject comprising administering a conventional immunosuppressant treatment using 15-deoxyspergualine. Applicants respectfully submit that US '490 teaches a tissue construct for implantation under the renal capsule of a mammal comprising a first tissue

component comprising functional thymic tissue and a second tissue component comprising a hematopoietic stromal microenvironment of the bone marrow in intimate association ("thy-marrow" composite). Page 4 of '490 teaches that in addition to the thy-marrow composite, conventional immunosuppressant treatment may be administered, e.g., 15-deoxyspergualine.

Citing *KSR International v. Teleflex, Inc.,* 82 USPQ 2d 1385 (U.S. 2007), the examiner has asserted that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective function and the combination would have yielded predictable results to one of ordinary skill in the art at the time the invention was made.

Applicants respectfully disagree. Under *KSR*, in formulating a rejection under 35 U.S.C.§ 103(a), based upon a combination of prior art elements, it remains necessary to identify the reasons why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed. 82 USPQ2d at 1396. In the instant case, there must be some reason why such a skilled artisan would have combined the administration of an anti-CD154 antibody (but not an anti-CD28 antibody) of the '282 patent with the administration of donor cells to a transplant recipient when WO '320 teaches donor cells administered prior to transplantation and/or first contacted with agents *in vitro*. Further, reasons need to be identified why an anti-CD154 antibody would be selected, but not a soluble form of CTLA4 or an anti-B7 or anti-B2 antibody (as also taught by the WO '320 patent). Absent such reasons, the presently claimed invention is not obvious and withdrawal of the rejection of claims 2 under 35 U.S.C. §103(a) is therefore warranted.

With respect to claim 13, there must be a reason why one skilled in the art would have ignored implantation of a thy-marrow composite of the '490 patent and combined administration to a transplant recipient of only bone marrow cells and 15-desoxypergualine with an anti-CD154 antibody (but not an anti-CD28 antibody) of the '282 patent when WO '320 teaches donor cells administered prior to transplantation or graft and/or contacted with agents *in vitro*. Further, reasons need to be identified why an anti-CD154 antibody would be selected, but not a soluble form of CTLA4 or an anti-B7 or anti-B2 antibody (as also taught by the WO '320 patent).

Alternatively with respect to claim 13, a reason must be identified why one skilled in the art would choose to administer 15 deoxyspergualine taught by US '209 with an anti-CD154 antibody (but not an anti-CD28 antibody) of the '282 patent with the administration of

donor cells to a transplant recipient when WO '320 teaches donor cells administered prior to transplantation and/or first contacted with agents *in vitro*. Further, reasons need to be identified why an anti-CD154 antibody would be selected, but not a soluble form of CTLA4 or an anti-B7 or anti-B2 antibody (as also taught by the WO '320 patent). Absent such reasons, the subject matter of claim 13 is not obvious and withdrawal of the rejection of claim 13 under 35 U.S.C. §103(a) is therefore warranted.

Accordingly, presently amended claims 2 and 13 and distinguished from, and non-obvious over, the cited prior art of record.

Respectfully submitted,

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